Houk-Jung
Organic Colloquium

"Writing the rules for targeting dynamic proteins"

Abstract:

Transcriptional coactivators and their partner transcription factors have been labeled as intrinsically disordered, fuzzy, and undruggable. We propose that the identification of conserved mechanisms of engagement between coactivators and their cognate activators should provide general principles for small-molecule modulator discovery. Towards that end, biophysical characterization of the structurally divergent coactivator Med25 reveals that it forms short-lived and dynamic complexes with three different transcriptional activators and that conformational shifts are mediated by a flexible substructure of two dynamical helices and flanking loops. Analogous substructures are found across eukaryotic coactivators. Further, targeting one of the flexible structures with a small molecule modulates Med25-activator complexes. Thus, the two conclusions of the work are actionable for the discovery of small-molecule modulators of this functionally important protein class.

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UCLA College | Physical Sciences Chemistry & Biochemistry

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4:00 PM | ZOOM

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